

R E M A R K S

The Applicants acknowledge the Office Action of March 29, 2005 with appreciation. Claims 29-58 and Claims 60-64 are pending in the application. Of these, Claims 29-44, 52-55, 60 and 61 are withdrawn from consideration. The Applicants request rejoinder of the withdrawn subject matter upon the Office determination of allowable subject matter in the elected invention. Claims 45-51, Claims 56-58 and Claims 62-64 are presently under examination.

To begin, the Office has withdrawn the rejection of Claims 50-51 under 35 U.S.C. § 112, first paragraph, for lack of enablement in view of the amendment to limit the claims to a method of treating cancers.

The Office has withdrawn the rejection of Claims 45-51, 56-58 and 62-64 under 35 U.S.C. § 112, second paragraph in view of the Applicants' remarks with regard to the appropriateness of the claim language "in need thereof".

The rejection of Claims 56-58, 63 and 64 for anticipation under 35 U.S.C. § 102(b) over d'Hinterland, et al., (U.S. Patent No. 4,501,693) is withdrawn in view of the amendment to clarify that the composition comprising proteoglycan is administered in combination with an anticancer treatment.

The Office maintains the rejection of Claims 45-49 and 62 under 35 U.S.C. § 103(a) as being obvious over d'Hinterland, et al. in view of Henderson, (U.S. Patent No. 5,648,478) and Teicher, et al., (U.S. Patent No. 5,776,898) and expands the rejection to apply to Claims 50-51, 56-58 and 63-64 in view of the amendments made with the Response of January 14, 2005.

The noted claims are rejected for obviousness because the Office considers d'Hinterland, et al. to disclose activation of NK cells by proteoglycans and Henderson to disclose that NK cells may be elicited to tumor cells.

With the Response and Amendment of January 14, 2005, the Applicants distinguished the instant invention from the cited prior art for the fact that Henderson discloses a tumor vaccine comprising an engineered expression system designed to specifically elicit NK cells to prostate tumor cells expressing the highly visible antigen. It was noted that there is no motivation for one skilled in the art to combine the reference teaching with the teaching of d'Hinterland, et al. and Teicher, et al. With the instant Action, the Office opines that the language of generic Claim 45, specifically the transitional phrase "comprising", does not exclude the use of a DNA tumor vaccine and that, therefore, Henderson anticipates the instant claims.

To further distinguish the instant invention from the disclosure of d'Hinterland, et al. and Henderson, the Applicants amend generic Claims 45 and 56 to include language defining the immune stimulation and/or induction of an antitumor response which is elicited by the instant proteoglycan preparation. Claim 45 is now drawn to a method of stimulating an immune response and/or inducing an antitumor immune response in a mammal, including a human, in need thereof, characterized by stimulation of proliferation of peripheral blood mononuclear cells, whereby a membrane fraction of Gram-negative bacteria, comprising proteoglycans, is administered in the form of a pharmaceutical composition in combination with an anticancer treatment in an amount effective to result in such induction and or stimulation. The stimulation of proliferation of PBMC's by the instant proteoglycan preparation is not disclosed, nor is it made obvious, by the prior art of record. The Applicants submit that with the instant amendment to include clarifying language, the cited prior art fail to teach each and every element of the claims to make a *prima facie* rejection for obviousness.

With regard to the instant amendment of Claims 45 and 56, the characteristic stimulation of proliferation of PBMC's elicited by the instant proteoglycan is discussed throughout the instant Specification. Furthermore, with the first Office Action on the merits, the Office makes reference to the *in vitro* proliferation of PBMC's and the production of TNF- α and IL-12 by blood monocytes. The Office acknowledges the Specificational teaching on page 4 of the Office Action of

December 23, 2003. The Office states that, "The specification further teaches that *in vitro* FMKp is an immunostimulant that induces the proliferation of PBMC from human blood that affects monocytes." Therefore, at the time the search was conducted, the surprising immunostimulant/antitumor performance characteristics of the instant invention was within the knowledge of the Office. Moreover, the Applicants discuss the surprising immunostimulant properties of the instant proteoglycan in the Response and Amendment of March 23, 2004 at page 3, second paragraph, and emphasize the advantages of the instant preparation to stimulate proliferation of immune cells which induce antitumor cytokines to augment traditional chemotherapy. Consequently, the instant amendment to include clarifying language drawn to the stimulation of proliferation of PBMC's is subject matter which has been under consideration throughout examination.

The d'Hinterland, et al. disclosure pertains to a distinctive proteoglycan preparation which confers a specific effect on NK cell activation (Column 2, line 21). A comparison of the galactose and protein content of the instant proteoglycan preparation (pages 15 and 19 of the instant Specification) with the proteoglycanic fraction of d'Hinterland, et al. (Column 2) demonstrates that these preparations are chemically distinct with respect to the galactose and protein content. d'Hinterland, et al. evaluate the immunostimulant qualities of the proteoglycan preparation and disclose that the most remarkable quality of the proteoglycanic fraction is the activation of the stimulation of N.K. cells (column 1, line 19).

With the instant Response, the Applicants amend Claims 45 and 56 to include language defining the physico-chemical characteristics of the instant proteoglycan to further distinguish over the d'Hinterland, et al. and Henderson disclosures. Dependent Claims 65 and 66 are presently added to the Listing of Claims to further define the physico-chemical characteristics of the instant proteoglycan. As noted above, support for the amendment and for new Claims 65 and 66 may be found in the instant Specification at page 14 and at page 19. The Applicants evaluate the immunostimulant qualities of the instant proteoglycan preparation and demonstrate that the instant proteoglycan, surprisingly, stimulates an immune response and/or

induces an antitumor response by the stimulation of proliferation of peripheral blood mononuclear cells. The instant proteoglycan induces an antitumor response by the induction of TNF- α and IL-12 cytokine secretion by monocytes, cytokines which are understood by those skilled in the art to possess antitumor effects. The demonstrated stimulation of proliferation of PBMC's by the instant proteoglycan is not synonymous with the NK cell stimulation, as disclosed in Figure 1 of d'Hinterland, et al. The cited references are silent as to stimulation of proliferation of PBMC's. Similarly, the cited references are silent as to stimulation of production of cytokines involved in tumor destruction. The instant proteoglycan preparation, having the defined proteoglycan composition, is demonstrated to stimulate an immune response and/or antitumor response through a mechanism which is not anticipated by the reference disclosure.

It is not obvious from the disclosure of d'Hinterland, et al., Henderson, et al. and Teicher, et al. that a membrane fraction comprising a proteoglycan, of a defined physico-chemical composition, through stimulation of proliferation of peripheral blood mononuclear cells, could enhance the therapeutic potential of chemotherapeutic agents or enhance an antitumor response. Therefore, the instant invention, as a whole, is not made obvious by the prior art of record. Reconsideration and withdrawal of the prior art rejection for obviousness is respectfully solicited.

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Accordingly, entry of the present amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding

insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,
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Enclosure: Listing of Claims and Postal Card Receipt.

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